REMARKS

The present application is directed to a method of producing a protective immune response in a mammal by administering to a lung of the mammal an aerosol containing a non-living reagent that produces the protective immune response in the mammal to which it is administered. Claims 17-25 and 28 are pending. Applicants amend Claim 28 to correct a typographical error.

Claim Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejects Claim 28 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claim, which was added in the Response to Non-Final Office Action filed November 6, 2008, contains new matter, namely, a limitation "biodegradable microspheres of an average diameter of from 0.5 to 5 mm." Applicants amend Claim 28 to correct an unintentional typographical error. Currently amended Claim 28 recites "an average diameter of from 0.5 to 5 μm." Applicants respectfully submit that the amendment to the claim overcomes the rejection and request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claim Rejection under 35 U.S.C. §103, second paragraph

Rejection of Claims 17-25 and 28 over Eyles in view of Zeng

The Examiner rejects Claims 17-25 and 28 under 35 U.S.C. §103(a) as obvious over Eyles *et al.* (*Vaccine,* 19:4732-4742 (2001); "Eyles") in view of Zeng *et al.*, *International Journal of Pharmaceutics*, 124:149-164 (1995); "Zeng"). Applicants respectfully traverse the rejection of the currently pending claims and assert that the currently pending claims would not have been obvious to one of ordinary skill in the art in the field of the present application at the time when applicants invented the claimed embodiments of the invention.

MPEP 2142 states: "To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention 'as a whole' would have been obvious at that time to that person." To reject a claim as obvious, the Examiner, first, must resolve the *Graham* factual inquires, namely, (a) determining the scope and content of the prior art, (b) ascertaining the differences between the claimed invention and the prior art, and (c) resolving the level of ordinary skill in the pertinent art. *See* MPEP 2141(II) citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

Eyles discloses the study of the immune responses in mice following nasal administration of a suspension of poly(lactide) microspheres loaded with recombinant *Yersinia pestis* V antigen. *See* Eyles, p. 4733, second column, section "Immunological studies." Eyles discloses data regarding antigen-specific proliferative responses and V antigen-specific antibody secreting cell numbers in the experimental animals following administration of the antigen-loaded microspheres, as well as cytokine production *in vitro* by splenocytes derived from the immunized mice. Eyles does not report any experimental data regarding protection of the animals following pathogen challenge.

Eyles also discloses the biodistribution data of non-biodegradable microspheres in mice following intranasal administration of a suspension of such microspheres. *See* Eyles, p. 4733, first column, section "Histological studies." Eyles states that "potentially significant quantity of non-biodegradable microparticulate material enters splenic tissue following bronchopulmonary deposition." *See* Eyles, p. 4740, second column, last paragraph. However, Eyles cautions that "[t]he implication of this finding for the design of mucosal immunisation [*sic*] strategies, particularly where vaccines are delivered to the lungs by aerosolisation … remains unclear" and that "there are also valid concerns about the safety of such an approach."

Zeng is a review article regarding controlled delivery of therapeutic drugs to the lung, including delivery of the drugs encapsulated in biodegradable microspheres. *See* Zeng, p. 154, section "Biodegradable microspheres," p. 155, section "Poly(glycolide and/or lactide) (PGL) microspheres." Zeng does not teach or suggest delivery of microencapsulated antigens for the purpose of producing a protective immune response, as recited in the pending claims.

Applicants have discovered that administration to the lung of experimental animals of an aerosol comprising biodegradable microspheres of an average diameter of from 0.5 to 5 μm comprising an antigen produces a protective immune response in the animals. Specifically, applicants discovered that administration of aerosolized antigen-loaded microspheres protects the experimental animals from a lethal challenge with *Y. pestis*. *See* specification of the present application, page 7, lines 5-11, pages 8-10, Example 1. Accordingly, applicants claim a method of producing a protective immune response against a pathogen in a mammal in need thereof, the method comprising administering to a lung of the mammal a protective amount of an aerosol comprising biodegradable microspheres of an average diameter of from 0.5 to 5 μm comprising a non-living reagent that produces a protective immune response against the pathogen in a mammal to whom it is administered, wherein administration of the aerosol to the lung produces a protective immune response against the pathogen in the mammal to whom it is administered (emphasis added).

Applicants respectfully assert that a combination of Eyles and Zeng fails to render obvious the currently pending claims at least in view of the differences between the claimed embodiments of applicants' invention and the disclosure provided in the cited articles. One of ordinary skill in the art in the vaccine field would not have found obvious the claimed method at least in view of the teaching in Eyles on the uncertainties and the safety concerns associated with delivery of microencapsulated vaccines to the lung and lack of experimental data regarding the ability of such vaccines to protect the experimental animals from a pathogen.

Zeng fails to add any knowledge relevant to one of ordinary skill in the art in the vaccine field, as Zeng concerns only therapeutic drugs and fails to discuss or suggest any methods of vaccine delivery. Contrary to the Examiner's comments in paragraph 7 of the Office Action, a person of ordinary skill in the art would not have found it obvious to combine the "aerosolization technique of Zeng et al in order to increase the efficacy of the composition of Eyles."

Furthermore, Eyles or Zeng fail to teach or suggest a method of producing a protective immune response against a pathogen in a mammal in need thereof, the method comprising administering to a lung of the mammal a protective amount of an aerosol comprising biodegradable microspheres of an average diameter of from 0.5 to 5 μm and comprising a non-living reagent that produces the protective immune response against the pathogen in the mammal, wherein the aerosol comprises the non-living reagent in a form encapsulated within the biodegradable microspheres and in a free non-encapsulated form, as recited in Claim 28. Applicants respectfully assert that a combination of Eyles and Zeng fails to render obvious Claim 28. Applicants respectfully bring to the Examiner's attention that no explanation was provided in the Office Action as to why one of ordinary skill in the art in the field of the present application would find Claim 28 obvious based on the teachings of Eyles or Zeng.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Claims 17-25 and 28 under 35 U.S.C. §103(a) as obvious over Eyles in view of Zeng.

Rejection of Claims 17-19, 22-25 and 28 over Lowell in view of Zeng

The Examiner rejects Claims 17-19, 22-25 and 28 under 35 U.S.C. §103(a) as obvious over Lowell *et al.* (*Infection and Immunity,* 64:1706-1713 (1996); "Lowell") in view of Zeng. Applicants respectfully traverse the rejection of the currently pending claims and assert that the currently pending claims would not have been obvious to one of ordinary skill in the art in the field of the present application at the time when applicants invented the claimed embodiments of the invention.

In the relevant parts, Lowell discloses intranasal administration to mice of a formulation comprising a formalinized toxoid of staphylococcal entertoxin B (SEB) and proteosomes. The formulation in Lowell was "instilled by micropipette into one or both nares." *See* Lowell, page 1707, sections "Proteosome vaccine formulation" and "Intranasal immunization." Lowell demonstrated that addition of proteosomes to SEB toxoid improved antitoxin immunity in the experimental animals. *See* Lowell, page 1711, section "Discussion." Lowell fails to teach of suggest a formulation comprising a microencapsulated antigen or administration of aerosol composition for the purpose of inducing protective immune response in an animal. The scope of content of Zeng is discussed in the previous section of this Response.

Applicants respectfully assert that a combination of Lowell and Zeng fails to render obvious currently pending claims at least in view of the differences between the claimed embodiments of applicants' invention and the disclosure provided in the cited articles. Applicants respectfully bring to the Examiner's attention that Lowell does not suggest microencapsulation as a way of improving immunogenicity of its vaccine compositions, using instead co-formulation with proteosomes, and does not suggest aerosol administration, relying instead on intranasal solution delivery. As discussed in the previous section of this Response, Zeng fails to teach or suggest microencapsulation of any immunogenic formulations. Accordingly, one of ordinary skill in the art in the vaccine field would not have found it obvious to combine the teaching of Zeng regarding microencapsulation and aerosol delivery of therapeutic compounds with the teaching of Lowell regarding intranasal delivery of vaccine solution in order to arrive at the claimed methods.

Furthermore, Lowell or Zeng fail to teach or suggest a method of producing a protective immune response against a pathogen in a mammal in need thereof, the method comprising administering to a lung of the mammal a protective amount of an aerosol comprising biodegradable microspheres of an average diameter of from 0.5 to 5 μm and comprising a non-living reagent that produces the protective immune response against the pathogen in the mammal, wherein the aerosol comprises the non-living reagent in a form

encapsulated within the biodegradable microspheres and in a free non-encapsulated form, as recited in Claim 28. Applicants respectfully assert that a combination of Lowell and Zeng fails to render obvious Claim 28 for at least this reason.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Claims 17-19, 22-25 and 28 under 35 U.S.C. §103(a) as obvious over Lowell in view of Zeng.

CONCLUSION

The foregoing is submitted as a full and complete response to the Office Action mailed January 15, 2009.

Applicants assert that the claims are in condition for allowance and respectfully request that the application be passed to issuance. If the Examiner believes that any informalities remain in the case that may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned agent at (404) 815-6102 or to Jamie L. Greene at (404) 745-2473 is respectfully solicited.

No additional fees are believed due; however the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account number 11-0855.

Respectfully submitted,

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